Therapeutic Management of Patients with COVID-19

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A number of investigational agents and drugs that are approved for other indications are currently being studied in clinical trials for the treatment of COVID-19 and associated complications. Data from randomized controlled trials, prospective and retrospective observational cohorts, and case series studies are rapidly emerging. The COVID-19 Treatment Guidelines Panel (the Panel) continues to review the most recent clinical data to provide up-to-date treatment recommendations to clinicians who are caring for patients with COVID-19. In this section, the Panel recommends strategies for managing patients with different severities of disease. A comprehensive summary of clinical data for drugs that are being investigated can be found in the Antiviral Therapy, Immune-Based Therapy, and Adjunctive Therapy sections of these Guidelines.

Figure 1. Recommendations for Pharmacologic Management of Patients with COVID-19 Based on Disease Severity

DISEASE SEVERITY	PANEL'S RECOMMENDATIONS *(Recommendations are listed in order of preference in each category below; however, all options are considered acceptable.)*
Not Hospitalized *or* **Hospitalized but Does Not Require Supplemental Oxygen**	No specific antiviral or immunomodulatory therapy recommended The Panel **recommends against** the use of **dexamethasone (AI)** See the Remdesivir section for a discussion of the data on using this drug in hospitalized patients with moderate COVID-19.[a]
Hospitalized and Requires Supplemental Oxygen **(but Does Not Require Oxygen Delivery Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or ECMO)**	**Remdesivir** 200 mg IV for one day, followed by remdesivir 100 mg IV once daily for 4 days or until hospital discharge, whichever comes first **(AI)**[b,c,d] *or* **Remdesivir** (dose and duration as above) plus **dexamethasone**[e] 6 mg IV or PO for up to 10 days or until hospital discharge, whichever comes first **(BIII)**[f] If **remdesivir** cannot be used, **dexamethasone**[e] may be used instead **(BIII)**
Hospitalized and Requires Oxygen Delivery Through a High-Flow Device or Noninvasive Ventilation	**Dexamethasone**[d] plus **remdesivir** at the doses and durations discussed above **(AIII)**[f] *or* **Dexamethasone**[d,e] at the dose and duration discussed above **(AI)**
Hospitalized and Requires Invasive Mechanical Ventilation or ECMO	**Dexamethasone**[d,e] at the dose and duration discussed above **(AI)** *or* **Dexamethasone**[e] plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**[f]

Rating of Recommendations: A = Strong; B = Moderate; C = Optional
Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

[a] The Panel recognizes that there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate COVID-19 (e.g., a patient who is at a particularly high risk for clinical deterioration). However, the Panel finds the data insufficient to recommend either for or against using remdesivir as routine treatment for all hospitalized patients with moderate COVID-19.
[b] Treatment duration may be extended to up to 10 days if there is no substantial clinical improvement by Day 5.
[c] The Panel recognizes there is a theoretical rationale for initiating remdesivir plus dexamethasone in patients with rapidly progressing COVID-19.
[d] For patients who are receiving remdesivir but progress to requiring oxygen through a high-flow device, noninvasive ventilation, invasive mechanical ventilation, or ECMO, remdesivir should be continued until the treatment course is completed.
[e] If dexamethasone is not available, equivalent doses of other corticosteroids, such as prednisone, methylprednisolone, or hydrocortisone, may be used. See Corticosteroids for more information.
[f] The combination of dexamethasone and remdesivir has not been studied in clinical trials; see text for the rationale for using this combination.

Key: ECMO = extracorporeal membrane oxygenation; IV = intravenously; PO = orally

For Patients with COVID-19 Who Are Not Hospitalized or Who Are Hospitalized With Moderate Disease but Do Not Require Supplemental Oxygen

Recommendations

- The Panel does not recommend any specific antiviral or immunomodulatory therapy for the treatment of COVID-19 in these patients. Patients are considered to have moderate disease if they have clinical or radiographic evidence of lower respiratory tract infection and a saturation of oxygen (SpO_2) ≥94% on room air at sea level.
- There are insufficient data for the Panel to recommend either for or against the use of remdesivir for the treatment of COVID-19.
- The Panel **recommends against** the use of **dexamethasone (AI)** or **other corticosteroids** for the treatment of COVID-19 **(AIII)** unless a patient has another clinical indication for corticosteroid therapy.

Additional Considerations

- The Panel recognizes there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., a person who is at a particularly high risk for clinical deterioration).

Rationale for Not Recommending Routine Use of Remdesivir in This Group of Patients

In the Adaptive COVID-19 Treatment Trial (ACTT-1), a multinational, randomized controlled trial that compared remdesivir to placebo in hospitalized patients with COVID-19, there was no observed benefit for remdesivir in patients with mild to moderate disease (defined as SpO_2 >94% on room air or a respiratory rate <24 breaths/min without supplemental oxygen).[1] In a manufacturer-sponsored, open-label, randomized trial of 596 patients with moderate COVID-19, patients who received 5 days of remdesivir had higher odds of a better clinical status on Day 11 than those who received standard care (OR 1.65; 95% CI, 1.09–2.48; $P = 0.02$). However, the difference between the groups was of uncertain clinical importance.

The Panel finds the available data insufficient to recommend either for or against routine treatment with remdesivir for all hospitalized patients with moderate COVID-19. However, the Panel recognizes there may be situations in which a clinician judges that remdesivir is an appropriate treatment for a hospitalized patient with moderate disease (e.g., a person who is at a particularly high risk for clinical deterioration).

Rationale for Recommending Against the Use of Corticosteroids in This Group of Patients

In the Randomised Evaluation of COVID-19 Therapy (RECOVERY) trial, a multicenter, open-label trial in the United Kingdom, hospitalized patients with COVID-19 were randomized to receive dexamethasone plus standard of care or standard of care alone (control arm).[2] Among participants who did not require supplemental oxygen at enrollment, no survival benefit was observed for dexamethasone: 17.8% participants in the dexamethasone arm and 14% in the control arm died within 28 days of enrollment (rate ratio 1.19; 95% CI, 0.91–1.55). Based on these data, the Panel **recommends against** the use of **dexamethasone** for the treatment of COVID-19 in this group of patients **(AI)**.

For Hospitalized Patients with COVID-19 Who Require Supplemental Oxygen but Who Do Not Require Delivery of Oxygen Through a High-Flow Device, Noninvasive Ventilation, Invasive Mechanical Ventilation, or Extracorporeal Membrane Oxygenation

Recommendations

The options below are listed in order of preference; however, all these options are considered acceptable.

- **Remdesivir** 200 mg intravenously (IV) for 1 day, followed by remdesivir 100 mg IV for 4 days or until hospital discharge, whichever comes first **(AI)**; *or*
- A combination of **remdesivir** (dose and duration as above) plus **dexamethasone** 6 mg IV or orally for up to 10 days or until hospital discharge **(BIII)**; *or*
- If remdesivir cannot be used, **dexamethasone** may be used instead **(BIII)**. See Remdesivir for more information.

Additional Considerations

- Remdesivir therapy may be extended to up to 10 days if no substantial clinical improvement is seen at Day 5.
- The combination of remdesivir and dexamethasone has not been studied in clinical trials; however, there are theoretical reasons for combining these drugs.
- The Panel recognizes there are theoretical reasons for adding dexamethasone to the drug regimen of patients who are currently receiving remdesivir but who are clinically deteriorating.
- If dexamethasone is not available, an alternative corticosteroid such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used **(BIII)**. See Corticosteroids for dosing recommendations.

Rationale for the Use of Remdesivir

In the final analysis of ACTT-1, remdesivir was associated with improved time to recovery (recovery rate ratio 1.45; 95% CI, 1.18–1.79) in a subgroup of 435 participants. In a post hoc analysis of deaths by Day 29, remdesivir appeared to confer a substantial survival benefit (HR for death 0.30; 95% CI, 0.14–0.64).1 For more information, please see Remdesivir Clinical Data.

Rationale for the Use of Dexamethasone

In the RECOVERY trial, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen but not invasive mechanical ventilation at enrollment; 23.3% of participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).[2] The amount of supplemental oxygen that participants were receiving and the proportions of participants who required oxygen delivery through high-flow devices or noninvasive ventilation were not specified. For more information, please see Corticosteroids.

The reason that routine dexamethasone monotherapy is not recommended is the theoretical concern that corticosteroids might slow viral clearance when they are administered without an antiviral drug. The results of an observational study suggest that delayed viral clearance may be a concern in patients with non-severe COVID-19 who are receiving corticosteroids without antiviral drugs. Corticosteroids have also been associated with delayed viral clearance and/or worse clinical outcomes in patients with other viral respiratory infections.[3-5]

Even though the RECOVERY trial did not specifically enroll participants with characteristics that would make them ineligible for remdesivir, based on the RECOVERY findings, the Panel recommends that **dexamethasone** may be used alone if remdesivir cannot be given **(BIII)**.

Rationale for the Use of Remdesivir Plus Dexamethasone

The safety and efficacy of using remdesivir plus dexamethasone for the treatment of COVID-19 has not been evaluated in clinical trials. Despite the lack of clinical trial data, there is a theoretical rationale for combining remdesivir and dexamethasone. Patients with severe COVID-19 may develop a systemic inflammatory response that leads to lung injury and multisystem organ dysfunction. The potent anti-inflammatory effects of corticosteroids might prevent or mitigate these hyperinflammatory effects. Thus, combining an antiviral with an anti-inflammatory agent may treat the viral infection as well as dampen the potentially injurious inflammatory response that is a consequence of the infection.

Based on these theoretical considerations, the Panel considers the combination of remdesivir and dexamethasone an option for patients in this group. Some experts would give remdesivir alone initially and limit the use of combination therapy to those who are clinically deteriorating while on remdesivir, those who show evidence of excess inflammation (e.g., based on laboratory parameters), and/or those who have other conditions that may confer a higher risk of disease progression.

For Hospitalized Patients with COVID-19 Who Require Delivery of Oxygen Through a High-Flow Device or Noninvasive Ventilation but Not Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

The options below are listed in order of preference; however, both options are considered acceptable.

- A combination of **dexamethasone** plus **remdesivir** at the doses and durations discussed above **(AIII)**; *or*
- **Dexamethasone** alone at the dose and duration discussed above **(AI)**.

Additional Considerations

- The combination of dexamethasone and remdesivir has not been studied in clinical trials. Because there are theoretical reasons for combining these drugs, the Panel considers both the combination of remdesivir and dexamethasone and dexamethasone alone to be acceptable options for treating COVID-19 in this group of patients.
- Because there is uncertainty regarding whether starting remdesivir confers clinical benefit in this group of patients, the Panel **does not recommend** using remdesivir alone.
- For patients who initially received remdesivir monotherapy and progressed to requiring high-flow oxygen supplementation or noninvasive ventilation, dexamethasone should be initiated and remdesivir should be continued until the treatment course is completed.
- If dexamethasone is not available, equivalent doses of other corticosteroids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** may be used **(BIII)**. See Corticosteroids for more information.

Rationale

In the RECOVERY Study, treatment with dexamethasone conferred a survival benefit among participants who required supplemental oxygen but not invasive mechanical ventilation at enrollment:

23.3% of the participants in the dexamethasone group died within 28 days of enrollment compared with 26.2% in the standard of care arm (rate ratio 0.82; 95% CI, 0.72–0.94).[2]

In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 1.09; 95% CI, 0.76–1.57) in the subgroup of participants who required high-flow oxygen or noninvasive ventilation at enrollment (n = 193). A post hoc analysis did not show a survival benefit at Day 29.[1] However, the trial was not powered to detect differences in outcomes within subgroups. Because there is uncertainty regarding the clinical benefit of using remdesivir alone in this subgroup, the Panel **does not recommend** using remdesivir monotherapy in these patients.

The combination of remdesivir and dexamethasone has not been studied in clinical trials; therefore, the safety and efficacy of this combination is unknown. Despite the lack of clinical trial data, the Panel recognizes that there are theoretical reasons to use dexamethasone and remdesivir in combination. One reason for coadministering remdesivir and dexamethasone is that antiviral therapy may decrease viral shedding or prevent the harmful clinical outcomes that have been observed in patients with other viral infections who have received steroids. In outbreaks of other coronavirus infections (e.g., Middle East respiratory syndrome [MERS] and severe acute respiratory syndrome [SARS]), corticosteroid use was associated with delayed virus clearance.[3,4] In cases of severe pneumonia caused by influenza, corticosteroid therapy appears to worsen clinical outcomes, including secondary bacterial infection and mortality.[5]

For Hospitalized Patients with COVID-19 Who Require Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation

Recommendations

The options below are listed in order of preference; however, both options are considered acceptable.

- **Dexamethasone** at the dose and duration discussed above **(AI)**; *or*
- **Dexamethasone** plus **remdesivir** for patients who have recently been intubated at the doses and durations discussed above **(CIII)**.

Additional Considerations

- The combination of dexamethasone and remdesivir has not been studied in clinical trials. There are theoretical reasons for coadministering these drugs in recently intubated patients.
- If dexamethasone is not available, alternative corticosteroids such as **prednisone**, **methylprednisolone**, or **hydrocortisone** can be used **(BIII)**. See Corticosteroids for dosing recommendations.
- For those who initially started remdesivir monotherapy and then progressed to mechanical ventilation or extracorporeal membrane oxygenation (ECMO), dexamethasone should be started and remdesivir should be continued to complete the treatment course.

Rationale

In the RECOVERY study, a survival benefit was seen for dexamethasone among participants who required invasive mechanical ventilation at randomization: 29.3% of participants in the dexamethasone group died within 28 days of enrollment compared with 41.4% in the control arm (rate ratio 0.64; 95% CI, 0.51–0.81). After the publication of the RECOVERY study, several smaller randomized trials were published that examined the role of corticosteroids in critically ill patients with COVID-19. A meta-analysis of seven randomized controlled trials compared the 28-day mortality of critically ill patients

with COVID-19 who received corticosteroids (dexamethasone, hydrocortisone, or methylprednisolone) to those who received the usual care or placebo. In this meta-analysis, 92% of the 1,703 patients evaluated were on invasive mechanical ventilation. Mortality was 32.7% in patients who were randomized to receive corticosteroids and 41.4% in patients who were randomized to receive the usual care or placebo (OR 0.66; 95% CI, 0.53–0.82). It should be noted that the RECOVERY trial accounted for 59% of the patients in this meta-analysis.[6]

The reason that dexamethasone is prioritized over remdesivir monotherapy is because there is uncertainty regarding the clinical benefit of using remdesivir in this group. In ACTT-1, there was no observed difference in time to recovery between the remdesivir and placebo groups (recovery rate ratio 0.98; 95% CI, 0.70–1.36) among participants who were on mechanical ventilation or ECMO at baseline (n = 285). In a post hoc analysis of deaths by Day 29, there was no evidence that remdesivir affected the mortality rate in this subgroup (HR 1.13; 95% CI, 0.67–1.89).[1] However, because the trial was not powered to detect differences in outcomes within subgroups, there is uncertainty about the effect of remdesivir on the course of COVID-19 in patients who are mechanically ventilated or on ECMO. There was no information available on the duration of mechanical ventilation in the study participants.

One theoretical reason for coadministering remdesivir and dexamethasone in patients who have recently been intubated is that antiviral therapy may prevent a steroid-related delay in viral clearance. This delay has been reported in previous studies when corticosteroids were given in the setting of other viral infections.[3,4] An observational study in people with non-severe COVID-19 suggested a similar delay in viral clearance in patients who received corticosteroids,[7] but these results have not been verified. Despite the lack of clinical trial data, some Panel members would coadminister dexamethasone and remdesivir in patients who have recently been placed on mechanical ventilation. Antivirals such as remdesivir might not have an impact later in the disease course because the rate of viral replication may be decreasing.

References

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